UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trad mark Offic
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

EXAMINER	
[illegible]	
ART UNIT	**PAPER NUMBER**
1632	8

DATE MAILED: 02/30/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Application No.	Applicant(s)
09/515 582	BUELOW E. T AL
Examiner	Art Unit
Q Janice Li	1632

Office Action Summary

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-25 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s).
18)☐ Interview Summary (PTO-413) Paper No.
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other

DETAILED ACTION

Claims 1-25 are pending and under examination in the current application.

Priority

The instant continuation-in-part application claims priority to parent application 09/216,005 and PCT/US99.30089. However, applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C.120 as follows:

The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971). The result section of working example 2 and figure 4 in the original disclosure (US 09/216,005) has been deleted, and replaced with new figures 4 and 5 in PCT/US99/30089 and the instant application. The working examples 3 and 4 are newly added in PCT/US99/30089, therefore, the instant disclosure is not the same as original disclosure, thus, the original disclosure is not enabling for the claimed invention. The priority date for claims drawn to methods of extending graft survival will be the filing date of PCT/US99/30089, i.e. December 16, 1999.

Drawings

The drawings are objected to under 37 CFR 1.83(a) because they fail to properly label the experimental groups shown in figure 4 as described in the specification. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14, and 16-22 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-12 are drawn to a method for extending survival of an organ transplant in a recipient using a nucleic acid that modulates heme oxygenase-I (HO-1) activity in cells. In analyzing whether a written description requirement is met for the claimed subject matter as a genus of nucleic acids that modulates HO-I activity, a representative number of species has to be disclosed by their complete structure and other relevant identifying characteristics, such as biological functions. However, neither the names, nor sequences/chemical structures of recited nucleic acids that modulate HO-I activity have been disclosed, one skilled artisan would not recognize that the applicants were in

possession of the claimed invention. Claims 2, 3, 4 are drawn to a nucleic acids encoding HO-I and derivatives, however, they fail to further limit claim 1, because these molecules encode HO-I and derivatives, not HO-1 modulators. Applicant is referred to the Revised Interim Guidelines for "Written Description" requirement published December 21, 1999 in the Federal Register, Volume 64, Number 244, pages 71427-71440. "POSSESSION MAY BE SHOWN IN ANY NUMBER OF WAYS. POSSESSION MAY BE SHOWN BY ACTUAL REDUCTION TO PRACTICE, BY A CLEAR DEPICTION OF THE INVENTION IN DETAILED DRAWINGS...OR BY A WRITTEN DESCRIPTION OF THE INVENTION DESCRIBING SUFFICIENT RELEVANT IDENTIFYING CHARACTERISTICS SUCH THAT A PERSON SKILLED IN THE ART WOULD RECOGNIZE THAT THE INVENTOR HAD POSSESSION OF THE CLAIMED INVENTION." (page 71435, middle column, first paragraph of "a") Adequate written description requires more than a mere statement that it is part of the invention. Without identifying characteristics of the recited nucleic acids having HO-I modulatory activity, it is not sufficient to show that a skilled artisan would recognize that the applicants were in possession of the claimed invention as a whole.

Claims 3 and 13, 14 are drawn to a group of nucleic acids having HO-1 activity or having at least 80% sequence identity to nucleotides 81-944 of SEQ ID NO:1 and having the biological activity of human HO-I. In view of the breadth of the claims when given the broadest, reasonable interpretation, these claims embrace a genus of polypepetides variants encoded by the polynucleotide having at least 80% sequence identity with SEQ ID NO:1. Considering the possible numbers of polypeptide variants, the art known knowledge is "EACH POSITION IN A PEPTIDE IS UNIQUELY DEFINED. THE NUMBER OF POSSIBLE PEPTIDES IS VERY LARGE. EVEN IN A RELATIVELY SHORT PEPTIDE. WHEN THE NUMBER OF

AMINO ACID UNITS IN THE PEPTIDE CHAIN EQUALS N, THE NUMBER OF POSSIBLE PEPTIDES IS 20^N. THE PREPARATION OF A SPECIFIC PEPTIDE SEQUENCE AND THE DETERMINATION OF THE SEQUENCE OF AMINO ACIDS IN A PEPTIDE OR PROTEIN CHAIN REQUIRES SPECIFICALLY ADAPTED CHEMICAL METHODS." (*Encyclopedia Britannica online*). In view of the state of the art in protein chemistry, it is probably one of the most unpredictable areas of biotechnology. Although the polynucleotide coding region determines amino acid sequence of the protein, it is the ability of three-dimensional structures that allows the protein to function and carry out the messages of the genome, in the instant case, having HO-1 activity. *Bowie et al* (Science 1990 Mar; 247:1306-10) teach certain position in the sequence are critical to the three dimensional structure/function relationship and these regions can tolerate only conservative substitutions or none at all (page 1306, column 2). In view of the state of the art and the level of the skill, the question is whether these polypeptide variants will have proper HO-1 activity. No art of record nor the instant specification teaches the structural-function relationship between these polypeptide variants and the polypeptide encoded by SEQ ID NO:1. One can not extrapolate the teachings of the specification to the scope of the claims because the skilled artisan cannot envision the detailed structure of polypeptides encompassed by these claims and whether they have biological function of human HO-I. *Rudinger* (Peptide Hormones 1976: June,pages 1-7) teaches the relationship of sequence components and the peptide hormone function and states "THE SIGNIFICANCE OF PARTICULAR AMINO ACIDS AND SEQUENCES FOR DIFFERENT ASPECTS OF BIOLOGICAL ACTIVITY CANNOT BE PREDICTED *A PRIORI* BUT MUST BE DETERMINED FROM CASE TO CASE BY PAINSTAKING EXPERIMENTAL STUDY." (last paragraph of text on page 6).

Weighing all factors in view of level of the skill and state of the art, a skilled artisian would not recognize from the disclosure that the applicant had the possession of claimed invention as a whole.

Claim 1-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for preservation of cell morphology in an *ex vivo* liver perfusion model, does not reasonably provide enablement for extending survival of *any* organ, *any type of transplant*, in *any recipient*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims

These claims are drawn to a method for extending the survival of an organ transplant in a recipient. Given the broadest reasonable interpretation, these claims embrace any type of transplant such as allograft or xenograft of any organ such as heart, kidney, in any recipient such as human.

The specification teaches transfection of Adv-HO-1 resulted an improved portal venous blood flow in a liver ischemia/reperfusion injury model *ex vivo*, and an extended animal survival in an *in vivo* experimental ischemia/isotransplantation liver (OLT model) in the rat model without hepatic artery reconstruction. Although the specification provides a working example of a rat liver transplant model wherein syngeneic liver transfected with Adv-HO-1 intravenously 24 hrs before harvest in the donor, the claimed invention is not enabled for the use in any recipient, any organ and any type of transplantation.

In view of the nature and the breadth of these claims, they are gene therapy methods for any organ transplants in any recipients. In view of the state of the art and the level of the skill, *Orkin et al.* (NIH Report, 1995 Dec) reviews the infant state of the art of gene therapy from before the instant invention was made. The overall conclusions were: 1) gene therapy for each disease would present its own scientific and clinical challenges; 2) no successful gene therapy protocol was known; 3) significant problems remained in all aspects of gene therapy, especially with respect to effective expression vectors; 4) one cannot predictably extrapolate the result of one animal model, such as mouse, to treatment of a disease in a different animal, such as human; and 6) assessment of known gene therapy protocols was hindered by poor gene transfer, reliance on qualitative, rather than quantitative assessments of gene transfer, lack of suitable controls and poor definition of biochemical or disease endpoints (pages 1-2). Although the reference is ages old, the general status of gene therapy art has not significantly changed. For example, gene therapy in cystic fibrosis and diabetes has been pioneer of the art. *Levine et al* (Mole Med Today 1999 Apr; 5:165-171) teach "A CAVEAT WITH ALL OF THESE STUDIES IS THAT THE IMMUNE RESPONSE IS ENORMOUSLY COMPLEX AND THAT SUBTLE DIFFERENCES BETWEEN SPECIES AND THE EXPERIMENTAL MODEL USED CAN RESULT IN DRAMATICALLY DIFFERENT RESULTS. FOR EXAMPLE, THERAPIES THAT PREVENT DIABETES IN RODENT MODELS OF DIABETES HAVE NOT BEDEN EFFICACIOUS IN HUMANS" (page 167, lines left column) *Boucher et al* (J Clin Invest 1999 Feb; 103:441-5) review that host cell resistance to foreign gene is another difficulty for successful gene therapy "DESPITE AN IMPRESSIVE AMOUNT OF RESEARCH IN THIS AREA, THERE IS LITTLE EVIDENCE TO SUGGEST THAT AN EFFECTIVE GENE-TRANSFER APPROACH FOR THE TREATMENT OF CF LUNG DISEASE IS IMMINENT. THE INABILITY

TO PRODUCE SUCH A THERAPY REFLECTS IN PART THE LEARNING CURVE WITH RESPECT TO VECTOR TECHNOLOGY AND THE FAILURE TO APPRECIATE THE CAPACITY OF THE AIRWAY EPITHELIAL CELLS TO DEFEND THEMSELVES AGAINST THE PENETRATION BY MOIETIES, INCLUDING GENE-THERAPY VECTORS, FROM THE OUTSIDE WORLD."

Applicant is reminded numerous factors complicating gene therapy, which have not been shown to be overcome by routine experimentation or resolved using animal models or *in vitro* studies. In the instant case, while the Ado-HO-1 extended the animal survival for certain time in the OLT model, the constantly present immune rejection of organ transplantation is excluded. The specification fails to provide evidence that this survival extension will occur in an allograft or xenograft model where a strong rejection response is expected, and whether the HO-1 protection will sustain the intense allograft and xenograft rejection response. In addition, the specification teaches to transfect the donor organ with Adv-HO-1 24 hours before transplantation via intravenous injection of the donor, this rarely can be done in human. Liver is also a special organ where abundant blood supplies is present, it would be easier to deliver the vector via thorough perfusion to many cells of the organ, it may not be the case for other solid organ. The rat model disclosed in the specification, without a hepatic artery reconstruction, is not a complete reflection of human situation. In view of the constant failure in extending promising animal study to clinical trials in the art pertain to gene therapy, it is evident that at the time of the invention, the gene therapy practitioner, while acknowledging the significant potential of gene therapy, still recognized that such therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings

within the specification for such therapeutic regiments. Although the instant specification provides an overview of a potential therapeutic use of the claimed vector, it is not enabled for its full scope because it only teaches a liver transplantation model. The specification does not disclose any other particular embodiments reduced to practice in any organ, such as a multi-cell type, multi-layered human kidney, whether the method will be enabled for extending graft survival of any organ, in any recipient. In summary, the teachings and guidance present in the specification, as a whole, represent an initial investigation into the feasibility of the development of a useful means executing gene therapy which awaits further development to the practical level. Based upon the limited disclosure, the unpredictability of the art, the level of the skill, and the breadth of the claims, one skill in the art would have been required to perform undue experimentation to practice the invention commensurate to its scope.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States

Claims 23-25 are rejected under 35 U.S.C. 102(b) as being anticipated by *Abraham et al* (Intl J Mole Med 1998 Apr; 1:657-63).

Abraham et al teach an adenoviral vector encoding HO-1 under a CMV promoter complexe to cationic liposomes. *Abraham et al* clearly anticipate these claims.

No claim is allowed. Claims 1-22 are free of prior art of the record because the prior art fails to teach using a HO-1 expression vector to extend survival of organ graft. However, they are subject to other rejections.

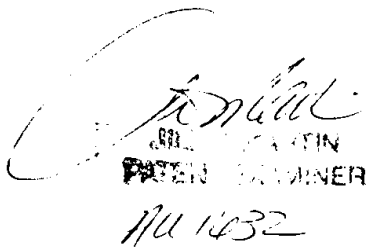
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942 The examiner can normally be reached on 8:30 am - 5 pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Karen M Hauda can be reached on 703-305-6608. The fax numbers for the organization where this application or proceeding is assigned are 703-308-8724 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Kay Pinsky, whose telephone number is (703) 305-3553

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632



QJL
March 26, 2001